U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control

| | Substitute f | or form 1449B/PTO | | Complete if Known | |
|---------|---------------------------------|----------------------|------------------------|-------------------|--|
| EB 0 5 | MILL INFORMAT | ION DISCLOSURE | Application Number | 09/120,383 | |
| LEB o s | | IT BY APPLICANT | Filing Date | 07/22/1998 | |
| 73 | Sata Submitt | ed: February 5, 2004 | First Named Inventor | Fumihiko Watanabe | |
| F TRAD! | ate Submitted: February 5, 2004 | | Group Art Unit | 1621 | |
| * /RAD | (use as many | sheets as necessary) | Examiner Name | Samuel Barts | |
| Sheet | 1 | of 4 | Attorney Docket Number | 67242/107 | |

| | U.S. PATENT DOCUMENTS | | | | | | | | |
|--------------------|--------------------------|---------------|---|---|------------------------------|--|--|--|--|
| Examiner Initials* | | U.S. Patent I | Document | - | Date of Publication of | Pages, Columns, Lines, Where Relevant | | | |
| | Cite No. ¹ | Number | Kind Code ² (if known) | Name of Patentee or Applicant of Cited Document | Cited Document MM-DD-YYYY | Passages or Relevant Figures Appear | | | |
| 3/3 | B1 | 3,784,701 | - | TOMCUFICIK ET AL | 01-09-1974 | | | | |
| 7 | B2 | 4,269,775 | | SZCZEPANSKI ET AL. | 05-26-1981 | | | | |
| | B3 | 4,388,464 | | KRISTINSSON ET AL. | 06-14-1983 | | | | |
| | B4 | 4,599,361 | | DICKENS ET AL. | 07-08-1986 | | | | |
| | B5 | 4,632,931 | | NAKANE | 12-30-1986 | | | | |
| | B6 | 4,715,883 | | LUKASZCZYK ET AL. | 12-29-1987 | | | | |
| | B7 | 5,270,326 | | GALARDY ET AL. | 12-14-1993 | | | | |
| | B8 | 6,294,674 | | PICARD | 09-25-2001 | | | | |
| 1 | B9 | 6,117,869 | | PICARD | 09-12-2000 | 1 | | | |
| 512 | B10 | 6,150,394 | | WATANABE ET AL. | 11-21-2000 | | | | |

| | | _ | | | | E/ | DREIGN PATENT DOCUMEN | Te | | |
|---|-----------------|----|--------------|----|-----------------|----|---|--|--|----------------|
| | xami iitials | | Cite No.1 | F | oreign Patent E | | Name of Patentee or Applicant of Cited Documents | Date of Publication of Cited Document MM-DD-YYYY | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T ⁶ |
| 5 | 51 | 13 | A1 | wo | 95/13064 | A1 | BRITISH BIOTECH PHARMACEUTICALS LIMITED | 05-18-1995 | · | |
| | 7 | 1 | B11 | EP | 305 947 | | MOCHIDA ET AL. | 03-08-1989 | | |
| | $\neg \Gamma$ | 0 | B12 | EP | 548 798 | | KURONO ET AL. | 06-30-1993 | | |
| | | ~ | B13 | EP | 606 046 | | MACPHERSON ET AL. | 07-13-1994 | | |
| Г | Т | V | B14 | wo | 94/12181 | | EGBERTSON ET AL. | 06-09-1994 | | |
| | \top | V | B15 | wo | 95/13289 | | MONTANA ET AL. | 05-18-1995 | | |
| Г | Т | V | B16 | wo | 95/35275 | | MILLER ET AL. | 12-28-1995 | | Ţ |
| | Т | U | B17 | wo | 95/35276 | | MILLER ET AL. | 12-28-1995 | | |
| | 7 | V | B18 | wo | 96/00214 | | MACPHERSON ET AL. | 01-04-1996 | | |
| | Т | V | B19 | wo | 96/11209 | | MONTANA ET AL. | 04-18-1996 | | |
| | T | 7 | B20 | wo | 96/15096 | | KLUENDER ET AL. | 05-23-1996 | | T |
| | T | V | B21 | wo | 93/14069 | | BOWLES ET AL. | 07-22-1993 | | |
| | 7 | V | B22 | wo | 97/45402 | | TAKAHASHI ET AL. | 12-04-1997 | | |
| Ī | T^{-} | V | B23 | EP | 757 037 | | SAKAKI ET AL. | 02-05-1997 | | |
| | П | 1 | B24 | EP | 757 984 | | SAKAKI ET AL. | 02-12-1997 | | |
| | 1 | ~ | B25 | EP | 468 231 | | ACKERMANN ET AL. | 01-29-1992 | | |
| 5 | 0 | 7 | B26 | JP | 57-59969 | | | 04-10-1982 | | |

| • | | NON PATENT LITERATURE DOCUMENTS | |
|--------------------|--------------------------|--|---|
| Examiner initials* | Cite No. ¹ | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published. | Ť |

| #1146083 | The state of the s | - Contract of the Contract of | | _ |
|-----------------------|--|---|----------|---|
| Examiner Signature | Stort | Date Considered | 11/18/04 | |
| | | | | _ |

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, PO Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, PO Box 1450, Alexandria, Virginia 22313-1450.

^{*}EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Unique citation designation number. ²See attached Kinds of U.S. Patent Documents. ³Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶Applicant is to place a check mark here if English language Translation is attached.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control

| 70 · · · ~ 4 | Substitute for form 1 | 449B/PTO | | Complete if Known | | | |
|--------------|-----------------------|---------------|------------------------|-------------------|-------------|--|--|
| (1 | RMATION DIS | CLOSURE | Application Number | 09/120,383 | | | |
| - n 5 2004 | TATEMENT BY A | PPLICANT | Filing Date | 07/22/1998 | | | |
| LED! O | Submitted: Febr | niany 5, 2004 | First Named Inventor | Fumihiko Watanabe | | | |
| λ . | 3/ | | Group Art Unit | 1621 | | | |
| The morning | as many sheets | as necessary) | Examiner Name | Samuel Barts | | | |
| Sheet | 2 | of 4 | Attorney Docket Number | 67242/107 | | | |

| | | | NON PATENT LITERATURE DOCUMENTS | |
|---------------|----|--------------------------|--|---|
| Initials* N | | Cite No. ¹ | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published. | Ţ |
| 5, | Bu | A2 | DATABASE CAPLUS 'Online!, CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN, Database accession no. 1993:626388, XP002230555, *abstract; RN 150782-45-9, 150782-77-7, 150782-48-2, 150782-51-7, 150782-72-2, 150782-47-1, 150782-49-3, 150782-50-6, 150782-73-3, 150782-70-0 * & M.H. EL-HAKIM: AL-AZHAR BULL. SCI., vol. 3, no. 1, 1992, pp. 9-17. | |
| | V | A3 | EL-SAYED, R.A., "Some novel sulfaniyl amino acid derivatives," J. SERB. CHEM. SOC., vol. 56, no. 6, 1991, pp. 311-318, XP000882133. | |
| | v | A4 | ROEMMELE ET AL., "Removal of N-Arylsulfonyl Groups from Hydroxy α-Amino Acids," J. ORG. CHEM., vol. 53, no. 10, 1988, pp. 2367-2371, XP002230552. | |
| | U | B27 | BEILSTEIN reference 5115437 | |
| | i | B28 | YE, ET AL., "Purification and Characterization of the Human Stromelysis Catalytic Domain Expressed in Escherichia coli," BIOCHEMISTRY, vol. 31, No. 45, pp. 11231-11235, 1992. | |
| | :/ | B29 | CHAPMAN ET AL., "Inhibition of Matrix Metalloproteinases by N-Carboxyalkyl Peptides," J. Med. Chem, vol. 36, No. 26, pp. 4293-4301, 1993. | |
| 1 | J | B30 | WILHELM ET AL., "SV40-transformed Human Lung Fibroblasts Secrete a 92-kDA Type IV Collagenase Which is Identical to That Secreted by Normal Human Macrophages," The JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 264, No. 29, pp. 17213-17221, 1989. | |
| | V | B31 | OKADA ET AL., "Matrix Metalloproteinase 9 (92-kDA Gelatinase/Type IV Collagenase) from HT 1080 Human Fibrosarcoma Cells," JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, No. 30, pp. 21712-21719, 1992. | |
| | V | B32 | WARD ET AL., "The Purification of Tissue Inhibitor of Metalloproteinases-2 from its 72 kDa Progelatinase Complex," BIOCHEMICAL JOURNAL, vol. 278, pp.179-187, 1991. | |
| | J | B33 | DEBNATH ET AL., "4-(4'-Substituted benzoyl) aminobenzenesulphonyl-L(+)glutamic acids and 5-N-substituted-2-[4'-(4"-substituted benzoyl)aminobenzenesulphonyl]-L-glutamines as potential antineoplastic agents: Synthesis, biological evaluation and quantitative structure-activity relational studies," INDIAN JOURNAL OF CHEMISTRY, vol. 28B, pp. 843-847, 1989. | |
| | Ü | B34 | GALLI ET AL., "Table II Enantiomeric Resolution of Dbs-Amino Acids on (S)-PheA-CSP," J. CHROMATOGR. A 666, pp. 77-89, 1994. | |
| 大人 | 5 | B35 | HANSEN ET AL., "Oxazoline Formation via a Palladium-catalyzed Cyclization: A Direct, Stereoselective Approach to cis-5-Amino-2-cyclopenten-1-ol Derivatives," Tetrahedron Letters, vol. 16, pp. 2913-2916, 1995. | |

| #1146083 | | | |
|-----------------------|-------|--------------------|----------|
| Examiner Signature | St Bd | Date Considered | 11/18/04 |

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, PO Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, PO Box 1450, Alexandria, Virginia 22313-1450.

^{*}EXAMINER: Inflial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Unique citation designation number. ²See attached Kinds of U.S. Patent Documents. ³Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶Applicant is to place a check mark here if English language Translation is attached.

MODIFIED PTO/SB/08 (08-00)

Approved for use through 10/31/2002. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control

| Substitute for form 1449B/PTO | | Complete if Known | |
|-------------------------------------|------------------------|-------------------|--|
| TOPODMATION DISCUSSION | Application Number | 09/120,383 | |
| STATEMENT BY APPLICANT | Filing Date | 07/22/1998 | |
| Date/Submitted: February 5, 2004 | First Named Inventor | Fumihiko Watanabe | |
| 4 | Group Art Unit | 1621 | |
| ((ee as many sheets as necessary) | Examiner Name | Samuel Barts | |
| Sheetanes 3 of 4 | Attorney Docket Number | 67242/107 | |

| | | NON PATENT LITERATURE DOCUMENTS | |
|-----------------------|--------------|--|---|
| Examiner Initials* | Cite No.1 | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published. | |
| M | B36 | HALVACEK ET AL., "An Alternative Route to N ^Q -Methylamino Acid Derivatives: Synthesis and Conformation of some N ^Q -Acetyl-N ^Q -Methylamino Acid Methylamides," Collection Czechoslovak Снем. Соммин., vol. 53, pp. 2473-2494, 1988. | |
| V | B37 | KAISER ET AL., "2-Substituted Derivative of 3,4-Dihydroxyphenylalanine," vol. 79, pp. 4365-4379, 1957. | |
| V | B38 | LEE ET AL., "Systematic study on the resolution of derivatized amino acids enantiomers on different cyclodextrin-bonded stationary phases," J. of Chromatography, 603, pp. 83-93, 1992. | _ |
| 1 | B39 | LIN ET AL., "Debsyl Chloride: Its Synthesis, Characterization and Application in Amino Acid and Amine Microanalysis," JOURNAL OF THE CHINESE BIOCHEMICAL SOCIETY, vol. 14, No. 1, pp. 10-19, 1985. | |
| ď | B40 | NATELSON ET AL., "Preparation of D-,DL-, and L-Homoserine Lactone from Methionine," MICROCHEMICAL JOURNAL 40, pp. 226-232, 1989. | |
| / | B41 | NICKEL ET AL., "Carboxylic acid analogues of suramin, potential filaricides," INDIAN JOURNAL OF CHEMISTRY, vol. 30B, pp. 182-187, 1991. | |
| J | B42 | STOCCHI ET AL., "Reversed-Phase High-Performance Liquid Chromatography Separation of Dimethylaminoazobenzene Sulfonyl-and Dimethtylaminoazobenzene Thiohydantoin-Amino Acid Derivative for Amino Acid Analysis and Microsequencing Studies at the Picomole Level," BIOCHEMISTRY, 178, pp. 107-117, 1989. | |
| V | B43 | VERDERAME, "Sulfide Derivatives of Cysteine II," JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 51, No. 6, pp. 576-579, 1962. | |
| 'n | B44 | YONEDA ET AL., "Reactions of L-α-Tosylamido-β-propiolactone: Synthesis, Reactions with Amines and Derivation to L-Seriene," UDC, vol. 89, pp. 98-103, 1969. | T |

| #1146083 | | | | | |
|-----------------------|-------|--------------------|----|-------|-----|
| Examiner Signature | St Bt | Date Considered | 11 | /18-1 | 104 |

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, PO Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, PO Box 1450, Alexandria, Virginia 22313-1450.

^{*}EXAMINER: Initial if reference considered. Whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Unique citation designation number. ²See attached Kinds of U.S. Patent Documents. ³Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶Applicant is to place a check mark here if English language Translation is attached.

T. . .

3

MODIFIED PTO/SB/08 (08-00)
Approved for use through 10/31/2002. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control

| T . | Substitute fo | | | Complete if Known | | | |
|---------|-----------------------------------|--------------|----------|------------------------|-------------------|--|--|
| P -~1 | INFORMATI SEATEMEN Submitte | ON DISCLO | SURE | Application Number | 09/120,383 | | |
| , 5 700 | SATEMEN | T BY APPL | ICANT | Filing Date | 07/22/1998 | | |
| 168 " | Submitte | d: Eabruan | 5 2004 | First Named Inventor | Fumihiko Watanabe | | |
| | Q =7 | | | Group Art Unit | 1621 | | |
| 7700 | se as many s | sheets as ne | cessary) | Examiner Name | Samuel Barts | | |
| Sheet | 4 | of | 4 | Attorney Docket Number | 67242/107 | | |

| | | NON PATENT LITERATURE DOCUMENTS | | | |
|-----------------------|--------------|---|--|--|--|
| Examiner Initials* | Cite No.1 | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published. | | | |
| 5k | B45 | KSANDER ET AL., "Dicarboxylic Acid Dipeptide Neutral Endopeptidase Inhibitors," J. Med. Chem., 38, pp. 1689-1700, 1995. | | | |
| V | B46 | SHIN-ZIKKENKAGAKUKOZA, vol. 14, 1787, 1978. | | | |
| V | B47 | HAMADA ET AL., "An Improved Synthesis of Arylsulfonyl Chlorides from Aryl Halides," Communications, pp. 852 – 854, 1986. | | | |
| √ | B48 | SONOGASHIRA ET AL., "A Convenient Synthesis of Acetylenes: Catalytic Substitutions of Acetylenic Hydrogen with Bromoalkenes, Iodoarenes, and Bromopyridines," TETRAHEDRON LETTERS, No. 50, pp. 4467 4470, 1975. | | | |
| , | B49 | SHARP ET AL., "Synthetic Connections to the Aromatic Directed Metalation Reaction. Unsymmetrical Biaryls by Palladium-Catalyzed Cross Coupling of Directed Metalation-Derived Arylboronic Acids with Halides," Tetrahedron Letters, vol. 26, No. 49, pp. 5997–6000, 1985. | | | |
| 1 | B50 | WITTIG ET AL., "Über Triphenyl-phosphin-methylene als olefinbildende Reagenzien (I. Mitteil.)," ALS OLEFINBILDENDE REAGENZIEN, No. 9, pp. 1318-1330, 1954. | | | |
| V | B51 | MORPHY, ET AL., "Matrix Metalloproteinase Inhibitors: Current Status," CURRENT MED. CHEM. 1995, vol. pp. 743-762, 1995. | | | |
| V | B52 | JG TOPLISS ET AL., <u>Drug Design</u> , (1975) Vol. 5, pp. 1-21 (Academic Press, London). | | | |
| 29 | B53 | OECD Guideline for the Testing of Chemicals. | | | |

| #1146083 | | | |
|-----------------------|-------|--------------------|----------|
| Examiner Signature | ef BA | Date Considered | 11/18/04 |

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief information Officer, U.S. Patent and Trademark Office, PO Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, PO Box 1450, Alexandria, Virginia 22313-1450.

^{*}EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Unique citation designation number. ²See attached Kinds of U.S. Patent Documents. ³Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶Applicant is to place a check mark here if English language Translation is attached.